

REMARKS

Claims 1-3, 7, 177-192 and 194-196 have been canceled without prejudice as being directed to non-elected subject matter. Claims 4-6, 8-176, 193-198 and 199-206 are pending.

The abstract has been amended to specifically recite the structure shown in Formula IV. Support for this amendment may be found, for example, in the specification as filed at page 15. Claims 4, 5, 8, 9, 26, 27, 30, 31, 32, 37, 38, 40, 42, 44, 46, 48, 50, 59, 62, 63, 161 and 169 have been amended to more clearly define the subject matter of the present invention, to correct typographical errors and to exclude non-elected subject matter. Claims 38, 40, 42, 46 and 48 have also been converted from dependent to independent format.

New claims 199-201 and 207, 210 and 211 have been added to specifically recite pharmaceutical compositions and packages comprising the compounds in claims 4 and 27. Support for these claims may be found, for example, in the specification at pages 34, and 47-51. Support for these claims is also found in original claims 180, 181, and 183. These latter claims are believed to have been inadvertently included in the non-elected group since they clearly fall within the scope of Group IV.

New claims 202-203 and 208-209 recite specific functional properties for the compounds of claims 4 and 27. Support for

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these claims may be found, for example, in the specification at page 36.

New claims 204, 205 and 206 recite the subject matter of canceled claims 24, 86 and 87, respectively, as independent claims. No new matter is added by any of the amendments herein.

The Examiner noted that the references listed on PTO form 1449 (Paper No. 5) are missing. Applicants submit copies of these references herewith, and request that the Examiner initial this PTO form 1449.

The Examiner is of the view that the abstract should contain a chemical structure. Applicants have amended the abstract to specifically recite Formula IV, and Applicants believe that this objection has been overcome.

Claims 4-6, 8, 30, 31 and 32-37 stand rejected under 35 U.S.C. §102(b) as being anticipated by Cho et al. (WO 98/00402). The Examiner is of the view that Cho et al. teaches the general preparation of piperazine derivatives in which a phenyl is linked to one piperazine nitrogen and a phenyl or pyridyl is attached to the other piperazine nitrogen via a carbonyl- or thiocarbonyl-containing linker. More specifically, the Examiner believes that certain compounds described by Cho et al. fall within the scope of the present claims.

Applicants respectfully traverse the rejection base on Cho et al. Cho et al. is directed to piperazine derivatives having

antitumor activity. The ring corresponding to Ar₂ of the claimed invention is phenyl, and the ring corresponding to Ar₁ of the claimed invention is substituted with a group ("Z") that is always *ortho* to the point of attachment and is limited in scope. Cho et al. does not teach or suggest compounds in which Ar₂ comprises a heteroatom, or in which Z is not present, and Cho et al. does not teach or suggest the use of such compounds as capsaicin receptor antagonists. Applicants have amended claims 4 and 31 to exclude compounds in which Ar₂ is phenyl. In claims 8 and 32, phenyl is not among the possible Ar₂ groups, and Applicants believe that no amendment of claims 8 and 32 is needed. Claims 27 and 30 have been amended to exclude compounds in which R₅ is hydroxyl, lower alkyl, lower alkoxy, piperazine, pyridyl or thienyl. Applicants submit that the rejection based on Cho et al. has been overcome.

Claims 4-6, 27, 28 and 32 stand rejected under 35 U.S.C. §102(b) as being anticipated by Bock et al. (U.S. Patent No. 5,756,504). In particular, the Examiner is of the view that Bock et al. teaches the synthesis of 1-(2,4-dimethoxyphenylacetyl)-4-(2-methylphenyl)piperazine. Applicants respectfully traverse this ground for rejection. Bock et al. is directed to oxytocin receptor antagonists, and does not teach or suggest compounds of the claimed invention. Applicants have amended claims 4 and 27 to exclude CR_BR_{B'} from the list of

possible A moieties. Claim 32 already recites that A is NH or O, and Applicants submit that no amendment of claim 32 is necessary. Applicants submit that the rejection based on Bock et al. has been overcome.

Claims 4-6 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kulagowski et al. (U.S. Patent No. 5,792,768). In particular, the Examiner asserts that Kulagowski et al. teaches the synthesis of 1-(2-benzimidazol-2-yl)acetyl-4-phenylpiperazine. Applicants respectfully traverse this rejection. Kulagowski et al. is directed to antipsychotic benzimidazole derivatives. The compounds recited therein contain a -CH₂- moiety at the position corresponding to A recited in the claims. As noted above, Applicants have amended claim 4 to exclude 'CR_BR_B' from the list of possible A moieties. Kulagowski et al. does not teach or suggest compounds in which A is one of the moieties recited within claim 4, as amended. Applicants submit that the rejection based on Kulagowski has been obviated.

Claims 4-6, 8-30, 31, 32-176 and 193-198 stand rejected under 35 USC §112, second paragraph, as being indefinite. In particular, the Examiner is of the view that the term "heterocycloalkyl" is not clear. Applicants respectfully traverse this rejection. Applicants believe the definition of this term in the specification at page 45 is clear. Those

skilled in the art would understand heterocycloalkyl, in view of the definition in the specification, to mean a cyclic system consisting of carbon atoms and at least one hetero atom, and where the heterocycloalkyl group is bound to the parent group by any of the ring members, unless otherwise specified. Nonetheless, to facilitate allowance, Applicants have amended claims 4, 5, 8, 9, 27, 31, 32 and 50 to replace the term "heterocycloalkyl" with "heterocycle," as suggested by the Examiner. Applicants request that this rejection be withdrawn.

Claims 194-196, directed to the manufacture of a medicament, have been canceled.

Finally, the Examiner is of the view that the phrase "the compound or salt is not addictive" in claim 193 is not clear. Applicants respectfully traverse this ground for rejection. The term "addictive" is well known in the art and is understood to refer to compounds that result in substance dependence when administered to a patient in a therapeutically effective amount. Criteria for establishing substance dependence are very specific, and are recited in, for example, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2000) pages 192-198, a copy of which is submitted herewith. Applicants believe that this ground for rejection has been overcome.

Applicants enclose herewith copies of the references cited in the PTO Form 1449 submitted previously.

Allowance of the elected claims is respectfully solicited. If the Examiner believes that discussion of the application will be helpful, the Examiner is encouraged to contact the undersigned attorney.

Respectfully submitted,

Dated: February 7, 2003

By:

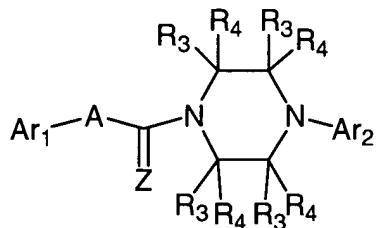


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Version with Markings to Show Changes Made

In the Abstract:

Disclosed are diaryl piperazines and related compounds of the following formula

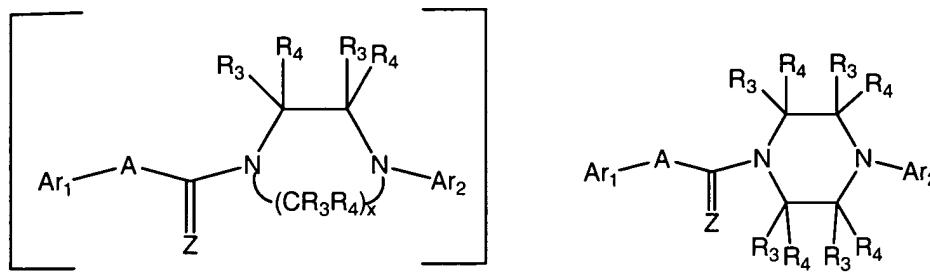


wherein the variables are as defined in the specification.

These compounds are selective modulators of capsaicin receptors, including human capsaicin receptors, that are, therefore, useful in the treatment of a chronic and acute pain conditions, itch and urinary incontinence. Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also provided. Compounds of the invention are also useful as probes for the localization of capsaicin receptors and as standards in assays for capsaicin receptor binding and capsaicin receptor mediated cation conductance. Methods of using the compounds in receptor localization studies are given.

In the Claims:

4. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S,

NR_A, [CR_BR_B',] NR_ACR_BR_B',

CR_B R_B'NR_A, -CR_A=CR_B-, and C₃H₄; where R_A, R_B, and R_B' are

independently selected at each occurrence from hydrogen

[or] and alkyl;

Z is oxygen or sulfur;

each R₃ and R₄ [are] is independently

(a) selected [at each occurrence] from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO[,]; optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio;

optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNHalkyl$; optionally substituted $-S(O)_nN(alkyl)(alkyl)$; optionally substituted $-NHC(=O)alkyl$; optionally substituted $-NC(=O)(alkyl)(alkyl)$; optionally substituted $-NHS(O)_nalkyl$; optionally substituted $-NS(O)_n(alkyl)(alkyl)$; optionally substituted saturated or partially unsaturated [heterocycloalkyl] heterocycle of from 5 to 8 atoms, which saturated or partially unsaturated [heterocycloalkyl] heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

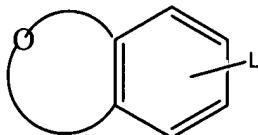
(b) [any two] joined to a R_3 [and] or R_4 not attached to the same carbon [may be joined] to form an optionally substituted aryl ring, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted, or a saturated, partially

unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

Ar₁ [and Ar₂ may be the same or different and are] is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R₅; [or] and

(b) [Ar₁ and Ar₂ may be the same or different and represent a] bicyclic oxygen-containing [group] groups of the formula:



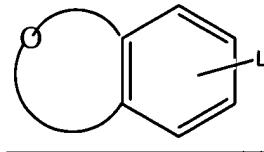
optionally mono-, di-, or trisubstituted with R₅, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8

ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

Ar₂ is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R₅; and

(b) bicyclic oxygen-containing groups of the formula:



optionally mono-, di-, or trisubstituted with R₅, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R₅ is independently selected at each occurrence from the group consisting of halogen, [cyano,] nitro, halo(C₁₋₆)alkyl,

halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆, C₂₋₆alkynyl substituted with 0-2 R₆, C₁₋₆alkoxy [substituted with 0-2 R₆, -NH(C₁₋₆alkyl) substituted with 0-2 R₆, -N(C₁₋₆alkyl)(C₁₋₆alkyl) where each C₁₋₆alkyl is independently substituted with 0-2 R₆, -XR₇,] and Y;

R₆ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, [-NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl),] -S(O)_n(C₁₋₄alkyl), halo(C₁₋₄)alkyl, halo(C₁₋₄)alkoxy, CO(C₁₋₄alkyl), CONH(C₁₋₄alkyl), CON(C₁₋₄alkyl₁)(C₁₋₄alkyl₂) where alkyl₁ and alkyl₂ may be joined to form a [heterocycloalkyl ring] heterocycle of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, -XR₇, and Y;

X is independently selected at each occurrence from the group consisting of -CH₂-, -CHR₈-, -O-, -S(O)_n-, -NH-, -NR₈-, -C(=O)-, -C(=O)O-, -C(=O)NH-, -C(=O)NR₈-, -S(O)_nNH-, -S(O)_nNR₈-, NHC(=O)-, -NR₈C(=O)-, -NHS(O)_n-, and -NR₈S(O)_n;

R₇ and R₈ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or

one or more double or triple bonds, each of which 1 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -NHS(O)_n(alkyl), -S(O)_n(alkyl), -S(O)_nN(alkyl₃)(alkyl₄) where alkyl₃ and alkyl₄ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio;

wherein said 3- to [8-memberered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2 [; and x is 1 or 3].

5. (Amended) A compound or salt according to Claim 4, wherein:

R_A , R_B , and R_B' are independently selected at each occurrence from hydrogen [or] and C_{1-6} alkyl; each R_3 and R_4 [are] is independently

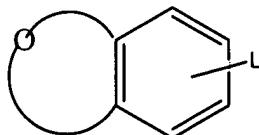
(a) chosen [at each occurrence] from the group consisting of hydrogen, halogen, cyano, nitro, $halo(C_{1-6})alkyl$, $halo(C_{1-6})alkoxy$, hydroxy, amino, C_{1-6} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 ; C_{2-6} alkynyl substituted with 0-2 R_6 ; C_{1-6} alkoxy substituted with 0-2 R_6 , $-NH(C_{1-6}alkyl)$ substituted with 0-2 R_6 , $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each C_{1-6} alkyl is independently substituted with 0-2 R_6 , $-XR_7$, and Y; or

(b) [any two] joined to a R_3 [and] or R_4 not attached to the same carbon [may be joined] to form an aryl ring substituted with 0-3 R_6 , a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R_6 , or a saturated, partially unsaturated, or aromatic heterocyclic ring of

from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R₆ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

[Ar₁ and Ar₂ may be the same or different and are selected from the group consisting of cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]ioxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R₅; or

Ar₁ and Ar₂ may be the same or different and represent a bicyclic oxygen-containing group of the formula:



optionally mono-, di-, or trisubstituted with R₅, where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8

ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of halogen, cyano, nitro, $\text{halo(C}_{1-6}\text{)alkyl}$, $\text{halo(C}_{1-6}\text{)alkoxy}$, hydroxy, amino, $C_{1-6}\text{alkyl}$ substituted with 0-2 R_6 , $C_{2-6}\text{alkenyl}$ substituted with 0-2 R_6 , and $C_{2-6}\text{alkynyl}$ substituted with 0-2 R_6 , $C_{1-6}\text{alkoxy}$ substituted with 0-2 R_6 , $-\text{NH(C}_{1-6}\text{alkyl)}$ substituted with 0-2 R_6 , $-\text{N(C}_{1-6}\text{alkyl})(C_{1-6}\text{alkyl})$ where each $C_{1-6}\text{alkyl}$ is independently substituted with 0-2 R_6 , $-\text{XR}_7$, and Y ;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, $C_{1-4}\text{alkyl}$, $C_{1-4}\text{alkoxy}$, $-\text{NH(C}_{1-4}\text{alkyl)}$, $-\text{N(C}_{1-4}\text{alkyl})(C_{1-4}\text{alkyl})$, $-\text{S(O)}_n(C_{1-4}\text{alkyl})$, $\text{halo(C}_{1-4}\text{)alkyl}$, $\text{halo(C}_{1-4}\text{)alkoxy}$, $\text{CO(C}_{1-4}\text{alkyl)}$, $\text{CONH(C}_{1-4}\text{alkyl)}$, $\text{CON(C}_{1-4}\text{alkyl}_1)(C_{1-4}\text{alkyl}_2)$ where alkyl₁ and alkyl₂ may be joined to form a heterocycloalkyl ring of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms selected from N, O, and S, $-\text{XR}_7$, and Y ;

X is independently selected at each occurrence from the group consisting of $-\text{CH}_2-$, $-\text{CHR}_8-$, $-\text{O}-$, $-\text{S(O)}_n-$, $-\text{NH}-$, $-\text{NR}_8-$, $-\text{C(=O)}-$, $-\text{C(=O)O}-$, $-\text{C(=O)NH}-$, $-\text{C(=O)NR}_8-$, $-\text{S(O)}_n\text{NH}-$, $-\text{S(O)}_n\text{NR}_8-$, $\text{NHC(=O)}-$, $-\text{NR}_8\text{C(=O)}-$, $-\text{NHS(O)}_n-$, and $-\text{NR}_8\text{S(O)}_n-$;

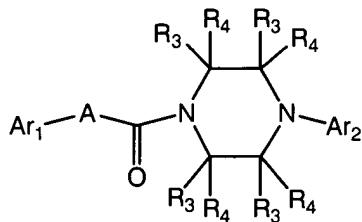
R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups,

and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NHS(O)_n(C₁₋₄alkyl), -S(O)_n(C₁₋₄alkyl), -S(O)_nNH(C₁₋₄alkyl), -S(O)_nN(C₁₋₄alkyl₃)(C₁₋₄alkyl₄) where C₁₋₄alkyl₃ and C₁₋₄alkyl₄ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y'; and

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which [may be further] are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, halo(C₁₋₄)alkyl, halo(C₁₋₄)alkoxy, mono- or di(C₁₋₄)alkylamino, and C₁₋₄alkylthio;

wherein said 3- to [8-membered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S [; n is independently chosen at each occurrence from 0, 1, and 2; and x is 1 or 3].

8. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:
A is absent or is selected from the group consisting of O, S, NR_A , $\text{CR}_B\text{R}_B'$, $\text{NR}_A\text{CR}_B\text{R}_B'$, $\text{CR}_B\text{R}_B'\text{NR}_A$, $-\text{CR}_A=\text{CR}_B-$, and C_3H_4 ; where R_A , R_B , and R_B' are independently selected at each occurrence from hydrogen or alkyl;

each R_3 and R_4 [are] is independently

(a) selected [at each occurrence] from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; $-\text{COOH}$; $-\text{CHO}$, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted

alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted $-S(O)_nNHalkyl$; optionally substituted $-S(O)_nN(alkyl)(alkyl)$; optionally substituted $-NHC(=O)alkyl$; optionally substituted $-NC(=O)(alkyl)(alkyl)$; optionally substituted $-NHS(O)_nalkyl$; optionally substituted $-NS(O)_n(alkyl)(alkyl)$; optionally substituted saturated or partially unsaturated [heterocycloalkyl] heterocycle of from 5 to 8 atoms, which saturated or partially unsaturated [heterocycloalkyl] heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S; optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

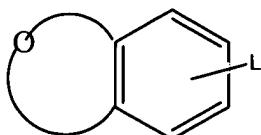
(b) [any two] joined to a R_3 [and] or R_4 not attached to the same carbon [may be joined] to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially

unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

Ar₁ and Ar₂ [may be the same or different and] are independently selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl; wherein Ar₁ is optionally mono-, di-, or trisubstituted with R₅, and Ar₂ is optionally mono-, di-, or trisubstituted with R₉; [or] and

(b) [Ar₁ and Ar₂ may be the same or different and represent a] bicyclic oxygen-containing [group] groups of the formula:



optionally mono-, di-, or trisubstituted with R₅, where L represents point of attachment and may be at any point on

the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6 , alkenyl substituted with 0-2 R_6 , alkynyl substituted with 0-2 R_6 , alkoxy [substituted with 0-2 R_6 , $-\text{NH}(\text{alkyl})$ substituted with 0-2 R_6 , $-\text{N}(\text{alkyl})(\text{alkyl})$ where each alkyl is independently substituted with 0-2 R_6 , $-\text{XR}_7$,] and Y ;

R_9 is independently selected at each occurrence from the group consisting of [cyano,] nitro, haloalkoxy, hydroxy, amino, alkyl substituted with 0-2 R_6 , alkenyl substituted with 0-2 R_6 , alkynyl substituted with 0-2 R_6 , alkoxy substituted with 0-2 R_6 , $[-\text{NH}(\text{alkyl})$ substituted with 0-2 R_6 , $-\text{N}(\text{alkyl})(\text{alkyl})$ where each alkyl is independently substituted with 0-2 R_6 , $-\text{XR}_7$,] and Y ;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl, alkoxy, $[-\text{NH}(\text{alkyl}), -\text{N}(\text{alkyl})(\text{alkyl}),] -\text{S}(\text{O})_n(\text{alkyl})$, haloalkyl, haloalkoxy, $\text{CO}(\text{alkyl})$, $\text{CONH}(\text{alkyl})$, $\text{CON}(\text{alkyl}_1)(\text{alkyl}_2)$ where alkyl₁ and alkyl₂ may be joined to form a [heterocycloalkyl ring] heterocycle of from 5 to 8 ring

atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, -XR₇, and Y;

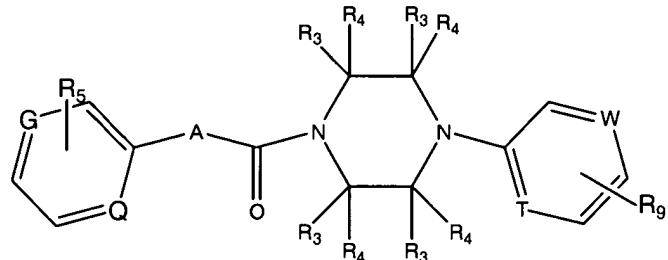
X is independently selected at each occurrence from the group consisting of -CH₂-, -CHR₈-, -O-, -S(O)_n-, -NH-, -NR₈-, -C(=O)-, -C(=O)O-, -C(=O)NH-, -C(=O)NR₈-, -S(O)_nNH-, -S(O)_nNR₈-, NHC(=O)-, -NR₈C(=O)-, -NHS(O)_n-, and -NR₈S(O)_n-;

R₇ and R₈ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -NHS(O)_n(alkyl), -S(O)_n(alkyl), -S(O)_nN(alkyl₃)(alkyl₄) where alkyl₃ and alkyl₄ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which [may be further] are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio; wherein said 3- to [8-membered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

9. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

G, Q, T, and W are the same or different and are selected from the group consisting of N, CH, and CR₅, wherein T or W or both is N;

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_{B'}, NR_ACR_BR_{B'}, CR_BR_{B'}NR_A, -CR_A=CR_B-, and C₃H₄; where

R_A , R_B , and R_B' are independently selected at each occurrence from hydrogen [or] and alkyl;

Z is oxygen or sulfur;

each R_3 and R_4 [are] is independently

(a) selected [at each occurrence] from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; $-COOH$; $-CHO$, optionally substituted C_{1-6} alkyl; optionally substituted C_{2-6} alkenyl; optionally substituted C_{2-6} alkynyl; optionally substituted C_{1-6} alkoxy; optionally substituted mono or di(C_{1-6})alkylamino; optionally substituted C_{1-6} alkylthio; optionally substituted C_{1-6} alkyl ketone; optionally substituted C_{1-6} alkylester; optionally substituted C_{1-6} alkylsulfinyl; optionally substituted C_{1-6} alkylsulfonyl; optionally substituted mono- or di(C_{1-6})alkylcarboxamide; optionally substituted $-S(O)_nNH$ C_{1-6} alkyl; optionally substituted $-S(O)_nN(C_{1-6}$ alkyl) (C_{1-6} alkyl); optionally substituted $-NHC(=O)$ C_{1-6} alkyl; optionally substituted $-NC(=O)$ (C_{1-6} alkyl) (C_{1-6} alkyl); optionally substituted $-NHS(O)_nC_{1-6}$ alkyl; optionally substituted $-NS(O)_n(C_{1-6}$ alkyl) (C_{1-6} alkyl); optionally substituted saturated or partially unsaturated [heterocycloalkyl] heterocycle of from 5 to 8 atoms, which saturated or partially unsaturated [heterocycloalkyl] heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

optionally substituted aryl having from 1 to 3 rings; and
optionally substituted heteroaryl, said heteroaryl having
from 1 to 3 rings, 5 to 8 ring members in each ring and, in
at least one of said rings, from 1 to about 3 heteroatoms
per ring independently selected from the group consisting
of N, O, and S; or

(b) [any two] joined to a R₃ [and] or R₄ not attached to
the same carbon [may be joined] to form an optionally
substituted aryl ring; a saturated or partially unsaturated
carbocyclic ring of from 5 to 8 members, which carbocyclic
ring is optionally substituted; or a saturated, partially
unsaturated, or aromatic heterocyclic ring of from 5 to 8
members, which heterocyclic ring is optionally substituted
and contains 1, 2, or 3 heteroatoms independently selected
from N, O, and S;

R₅ represents 1 to 3 substituents [and is] independently selected
at each occurrence from the group consisting of cyano,
hydroxy, amino, C₃₋₆ alkyl substituted with 0-2 R₆, C₂₋₆
alkenyl substituted with 0-2 R₆, C₂₋₆ alkynyl substituted
with 0-2 R₆, C₃₋₆ alkoxy [substituted with 0-2 R₆], -NH(C₁₋₆alkyl)
substituted with 0-2 R₆, -N(C₁₋₆alkyl)(C₁₋₆alkyl)
where each alkyl is independently substituted with 0-2 R₆,
-XR₇, and Y;

R_9 represents 0 to 3 substituents [and is] independently selected at each occurrence from the group consisting of halogen, [cyano,] nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 , C_{2-6} alkynyl substituted with 0-2 R_6 , C_{1-6} alkoxy substituted with 0-2 R_6 , $[-NH(C_{1-6}alkyl)]$ substituted with 0-2 R_6 , $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each C_{1-6} alkyl is independently substituted with 0-2 R_6 , $-XR_7$,] and Y ;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $[-NH(C_{1-4}alkyl)]$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$,] $-S(O)_n(C_{1-4}alkyl)$, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-4}alkyl_1)(C_{1-4}alkyl_2)$ where alkyl₁ and alkyl₂ may be joined to form a [heterocycloalkyl ring] heterocycle of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y ;

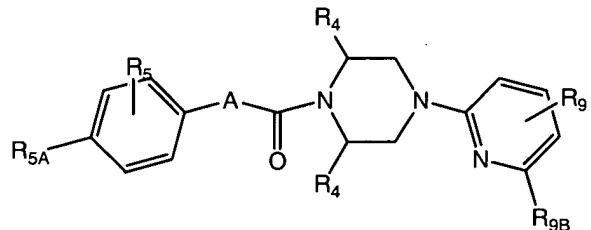
X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups,

and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, $-O(C_{1-4}\text{alkyl})$, $-NH(C_{1-4}\text{alkyl})$, $-N(C_{1-4}\text{alkyl})(C_{1-4}\text{alkyl})$, $-NHC(O)(C_{1-4}\text{alkyl})$, $-N(C_{1-4}\text{alkyl})C(O)(C_{1-4}\text{alkyl})$, $-NHS(O)_n(C_{1-4}\text{alkyl})$, $-S(O)_n(C_{1-4}\text{alkyl})$, $-S(O)_nNH(C_{1-4}\text{alkyl})$, $-S(O)_nN(C_{1-4}\text{alkyl}_3)(C_{1-4}\text{alkyl}_4)$ where $C_{1-4}\text{alkyl}_3$ and $C_{1-4}\text{alkyl}_4$ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y'; Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which [may be further] are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, $C_{1-4}\text{alkyl}$, $C_{1-4}\text{alkoxy}$, $\text{halo}(C_{1-4})\text{alkyl}$, $\text{halo}(C_{1-4})\text{alkoxy}$, mono- or di(C_{1-4})alkylamino, and $C_{1-4}\text{alkylthio}$;

wherein said 3- to [8-membered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and n is independently chosen at each occurrence from 0, 1, and 2.

26. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and CH₂NH;

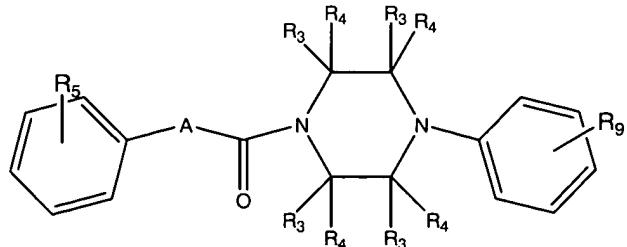
R₄ is independently chosen from hydrogen and C₁₋₄ alkyl;

R₅ represents 0 to 2 substituents [and is] independently chosen at each occurrence from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆, C₂₋₆alkynyl substituted with 0-2 R₆, C₁₋₆alkoxy [substituted with 0-2 R₆], -NH(C₁₋₆alkyl) substituted with 0-2 R₆, and -N(C₁₋₆alkyl)(C₁₋₆alkyl) where each C₁₋₆alkyl is independently substituted with 0-2 R₆;

R₉ represents 0 to 2 substituents and is independently chosen at each occurrence from the group consisting of halogen,

[cyano,] nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆, C₂₋₆alkynyl substituted with 0-2 R₆, and C₁₋₆alkoxy substituted with 0-2 R₆ [, -NH(C₁₋₆alkyl) substituted with 0-2 R₆, and -N(C₁₋₆alkyl)(C₁₋₆alkyl) where each C₁₋₆alkyl is independently substituted with 0-2 R₆]; R_{5A} is independently selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆ alkyl, C₁₋₆ alkoxy, -NH(C₁₋₆ alkyl), and -N(C₁₋₆ alkyl) (C₁₋₆ alkyl); R_{9B} is independently selected from the group consisting of halogen, nitro, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆ alkyl, and C₁₋₆ alkoxy [, -NH(C₁₋₆ alkyl), and -N(C₁₋₆ alkyl) (C₁₋₆ alkyl)]; and R₆ is independently selected at each occurrence the group consisting of halogen, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, -NH(C₁₋₄ alkyl), and -N(C₁₋₄ alkyl) (C₁₋₄ alkyl).

27. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of a single bond, S, NR_A, [CHR_B,] NR_ACHR_B, CHR_BNR_A, -CR_A=CR_B- , and C₃H₄; where R_A and R_B are independently selected at each occurrence from the group consisting of hydrogen and alkyl; each R₃ and R₄ [are] is independently

(a) selected [at each occurrence] from the group consisting of hydrogen; halogen; hydroxy; amino; cyano; nitro; -COOH; -CHO, optionally substituted alkyl; optionally substituted alkenyl; optionally substituted alkynyl; optionally substituted alkoxy; optionally substituted mono or dialkylamino; optionally substituted alkylthio; optionally substituted alkyl ketone; optionally substituted alkylester; optionally substituted alkylsulfinyl; optionally substituted alkylsulfonyl; optionally substituted mono- or di-alkylcarboxamide; optionally substituted -S(O)_nNHalkyl; optionally substituted -S(O)_nN(alkyl)(alkyl); optionally substituted -NHC(=O)alkyl; optionally substituted -NC(=O)(alkyl)(alkyl); optionally substituted -NHS(O)_nalkyl; optionally substituted -NS(O)_n(alkyl)(alkyl); optionally substituted saturated or partially unsaturated [heterocycloalkyl] heterocycle of from 5 to 8 atoms, which saturated or partially unsaturated [heterocycloalkyl] heterocycle contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

optionally substituted aryl having from 1 to 3 rings; and optionally substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 8 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms per ring independently selected from the group consisting of N, O, and S; or

(b) [any two] joined to a R₃ [and] or R₄ not attached to the same carbon [may be joined] to form an optionally substituted aryl ring; a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is optionally substituted; or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is optionally substituted and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

R₅ [is] represents 0-3 substituents independently selected at each occurrence from the group consisting of cyano, nitro, haloalkyl, haloalkoxy, [C₁₋₆ alkyl substituted with 0-2 R₆,] C₂₋₆ alkenyl substituted with 0-2 R₆, and C₂₋₆ alkynyl substituted with 0-2 R₆ [,C₁₋₆ alkoxy substituted with 0-2 R₆, -NH(C₁₋₆ alkyl) substituted with 0-2 R₆, -N(C₁₋₆ alkyl)(C₁₋₆ alkyl) where each alkyl is independently substituted with 0-2 R₆, -XR₇, and Y];

R_9 represents 0-3 substituents [and is] independently selected at each occurrence from the group consisting of bromo, haloalkyl, haloalkoxy, hydroxy, C_{2-6} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 , C_{2-6} alkynyl substituted with 0-2 R_6 , and C_{2-6} alkoxy [substituted with 0-2 R_6 , $-NH(C_{2-6}$ alkyl) substituted with 0-2 R_6 , $-N(C_{2-6}$ alkyl)(C_{2-6} alkyl) where each C_{2-6} alkyl is independently substituted with 0-2 R_6 , $-XR_7$, and Y];

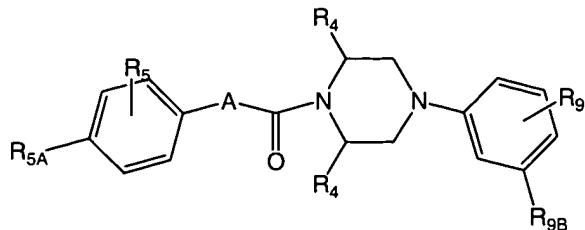
R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, alkyl, alkoxy, $[-NH(alkyl)$, $-N(alkyl)(alkyl)$,] $-S(O)_n(alkyl)$, haloalkyl, haloalkoxy, $CO(alkyl)$, $CONH(alkyl)$, $CON(alkyl_1)(alkyl_2)$ where $alkyl_1$ and $alkyl_2$ may be joined to form a [heterocycloalkyl ring] heterocycle of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y ;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups

consisting of 3 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 3 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -NHS(O)_n(alkyl), -S(O)_n(alkyl), -S(O)_nNH(alkyl), -S(O)_nN(alkyl₃)(alkyl₄) where alkyl₃ and alkyl₄ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y'; Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which [may be further] are unsubstituted or substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, alkyl, alkoxy, haloalkyl, haloalkoxy, mono- or dialkylamino, and alkylthio; wherein said 3- to [8-membered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and n is independently chosen at each occurrence from 0, 1, and 2.

30. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of NH, -CH=CH-, and CH₂NH;

R₄ is independently selected at each occurrence from hydrogen and C₁₋₄alkyl;

R₅ represents 0 to 2 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, [hydroxy,] amino, [C₁₋₆alkyl substituted with 0-2 R₆,] C₂₋₆alkenyl substituted with 0-2 R₆, and C₂₋₆alkynyl substituted with 0-2 R₆ [, C₁₋₆alkoxy substituted with 0-2 R₆, -NH(C₁₋₆alkyl) substituted with 0-2 R₆, and -N(C₁₋₆alkyl)(C₁₋₆alkyl), where each C₁₋₆alkyl is independently substituted with 0-2 R₆];

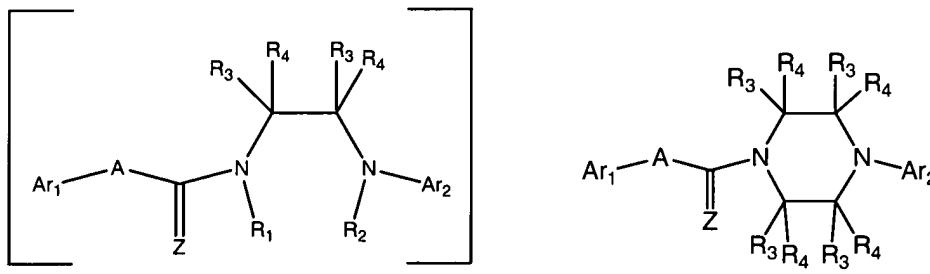
R₉ represents 0 to 2 substituents and is independently selected at each occurrence from the group consisting of halogen, [cyano,] nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆, C₂₋₆alkynyl substituted with 0-2 R₆,

and C_{1-6} alkoxy substituted with 0-2 R_6 [, $-\text{NH}(C_{1-6}\text{alkyl})$ substituted with 0-2 R_6 , and $-\text{N}(C_{1-6}\text{alkyl})(C_{1-6}\text{alkyl})$ where each $C_{1-6}\text{alkyl}$ is independently substituted with 0-2 R_6], R_{5A} is independently selected from the group consisting of halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, amino, C_{1-6} alkyl, C_{1-6} alkoxy, $-\text{NH}(C_{1-6}\text{ alkyl})$, and $-\text{N}(C_{1-6}\text{ alkyl})(C_{1-6}\text{ alkyl})$;

R_{9B} is independently selected from the group consisting of trifluoromethoxy, hydroxy, C_{2-6} alkyl, and C_{2-6} alkoxy [, $-\text{NH}(C_{2-6}\text{ alkyl})$, and $-\text{N}(C_{2-6}\text{ alkyl})(C_{2-6}\text{ alkyl})$]; and

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, C_{1-4} alkyl, and C_{1-4} alkoxy [, $-\text{NH}(C_{1-4}\text{ alkyl})$, and $-\text{N}(C_{1-4}\text{ alkyl})(C_{1-4}\text{ alkyl})$].

31. (Amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein the compound or pharmaceutically acceptable salt thereof exhibits an EC50 or K_i of 1 micromolar or less in a standard

assay of capsaicin receptor mediated calcium mobilization;
and wherein

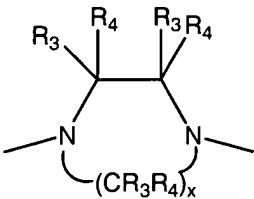
A is absent or is selected from the group consisting of O, S,

NR_A, [CR_BR_B',] NR_ACR_BR_B',

CR_B R_B'NR_A, -CR_A=CR_B-, and C₃H₄; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen [or] and C₁₋₆ alkyl;

Z is oxygen or sulfur;

[R₁ and R₂ independently represent hydrogen or C₁₋₆ alkyl; or R₁ and R₂ are taken together to form a 5 to 8 membered nitrogen-containing ring of the formula:



wherein x is 1, 2, or 3;]

each R₃ and R₄ [are] is independently

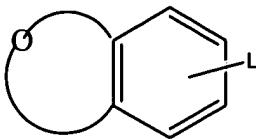
(a) selected [at each occurrence] from the group consisting of hydrogen, halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆; C₂₋₆alkynyl substituted with 0-2 R₆; C₁₋₆alkoxy substituted with 0-2 R₆, -NH(C₁₋₆alkyl) substituted with 0-2 R₆, -N(C₁₋₆alkyl)(C₁₋₆alkyl) where each C₁₋₆alkyl is independently substituted with 0-2 R₆, -XR₇, and Y; or

(b) [any two] joined to a R₃ [and] or R₄ not attached to the same carbon [may be are joined] to form an aryl ring substituted with 0-3 R₆, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R₆, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R₆ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

Ar₁ [and Ar₂ may be the same or different and are] is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R₅; [or] and

(b) [Ar₁ and Ar₂ may be the same or different and represent a] bicyclic oxygen-containing [group] groups of the formula:

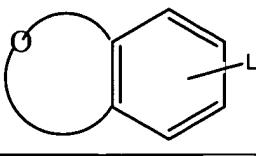


optionally mono-, di-, or trisubstituted with R_5 , where L represents point of attachment and may be at any point on the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

Ar₂ is selected from the group consisting of:

(a) cyclohexyl, cyclopentyl, piperidinyl, piperazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and quinoxalinyl, each of which is optionally mono-, di-, or trisubstituted with R_5 ; and

(b) bicyclic oxygen-containing groups of the formula:



optionally mono-, di-, or trisubstituted with R_5 , where L represents point of attachment and may be at any point on

the benzene ring, and the oxygen-containing ring of the bicyclic oxygen-containing group consists of from 5 to 8 ring atoms, contains 1 or 2 oxygen atoms and remaining ring atoms are carbon;

R_5 is independently selected at each occurrence from the group consisting of halogen, [cyano,] nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 , C_{2-6} alkynyl substituted with 0-2 R_6 , C_{1-6} alkoxy [substituted with 0-2 R_6 , $-NH(C_{1-6}alkyl)$ substituted with 0-2 R_6 , $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$ where each C_{1-6} alkyl is independently substituted with 0-2 R_6 , $-XR_7$], and Y ;

R_6 is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $[-NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl),] -S(O)_n(C_{1-4}alkyl)$, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, $CO(C_{1-4}alkyl)$, $CONH(C_{1-4}alkyl)$, $CON(C_{1-4}alkyl_1)(C_{1-4}alkyl_2)$ where alkyl₁ and alkyl₂ may be joined to form a [heterocycloalkyl ring] heterocycle of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, $-XR_7$, and Y ;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_8-$, $-O-$, $-S(O)_n-$, $-NH-$, $-NR_8-$, -

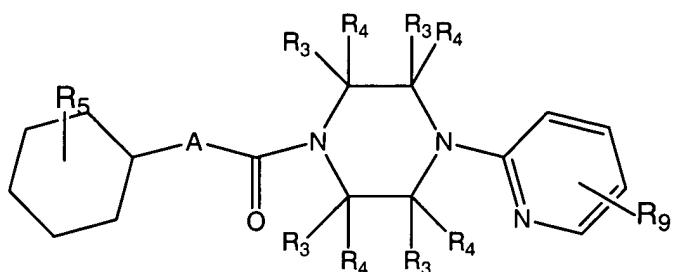
$C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, $-C(=O)NR_8-$, $-S(O)_nNH-$, $-S(O)_nNR_8-$, $NHC(=O)-$, $-NR_8C(=O)-$, $-NHS(O)_n-$, and $-NR_8S(O)_n-$;

R_7 and R_8 are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, $-O(C_{1-4}alkyl)$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NHC(O)(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)C(O)(C_{1-4}alkyl)$, $-NHS(O)_n(C_{1-4}alkyl)$, $-S(O)_n(C_{1-4}alkyl)$, $-S(O)_nNH(C_{1-4}alkyl)$, $-S(O)_nN(C_{1-4}alkyl_3)(C_{1-4}alkyl_4)$ where $C_{1-4}alkyl_3$ and $C_{1-4}alkyl_4$ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

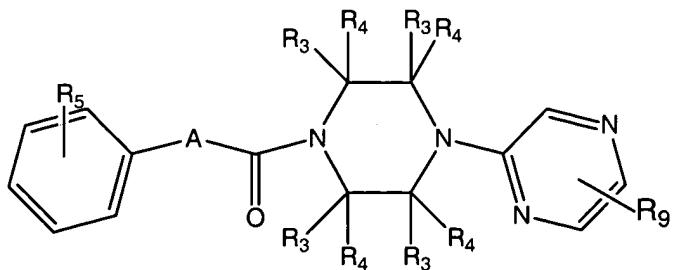
Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano,

C_{1-4} alkyl, C_{1-4} alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4} alkylthio; wherein said 3- to [8-memberered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and n is independently chosen at each occurrence from 0, 1, and 2.

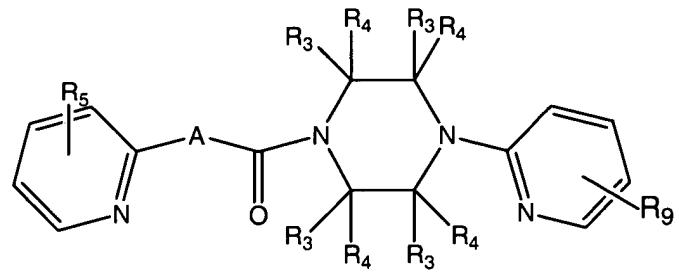
32. (Amended) A compound of the Formula A, Formula B, Formula C, Formula D, Formula E, or Formula F:



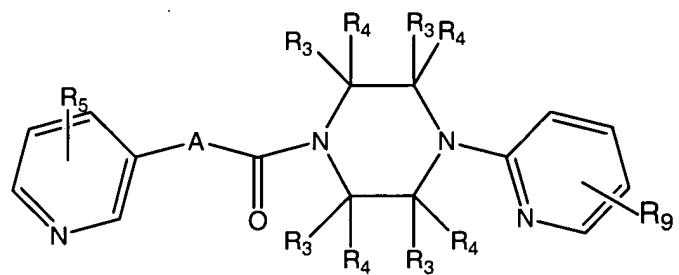
Formula A



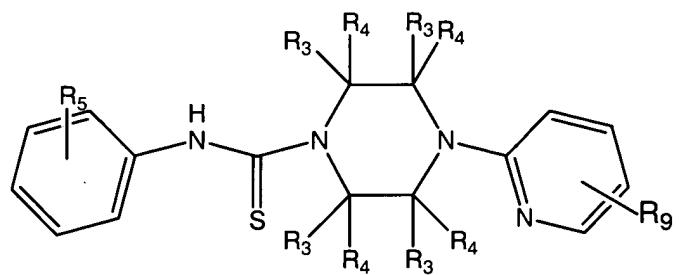
Formula B



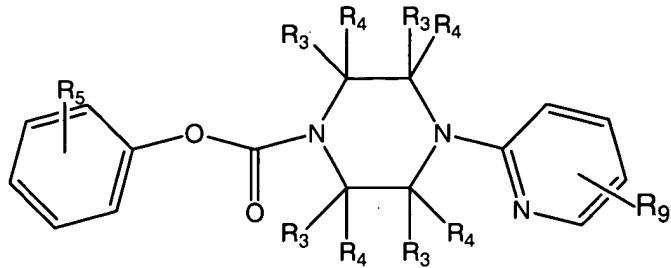
Formula C



Formula D



Formula E



Formula F

or a pharmaceutically acceptable salt of Formula A, Formula B, Formula C, Formula D, Formula E, or Formula F, wherein A represents NH or O;

each R₃ and R₄ [are] is independently

(a) selected [at each occurrence] from the group consisting of hydrogen, halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆; C₂₋₆alkynyl substituted with 0-2 R₆; C₁₋₆alkoxy substituted with 0-2 R₆, -NH(C₁₋₆alkyl) substituted with 0-2 R₆, -N(C₁₋₆alkyl)(C₁₋₆alkyl) where each C₁₋₆alkyl is independently substituted with 0-2 R₆, -XR₇, and Y; or

(b) [any two] joined to a R₃ [and] or R₄ not attached to the same carbon [may be joined] to form an aryl ring substituted with 0-3 R₆, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R₆, or a saturated, partially unsaturated, or aromatic heterocyclic ring of

from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R₆ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

R₅ [and R₉ each represent] represents from 1 to 3 substituents [and are] independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C₁-₆)alkyl, halo(C₁-₆)alkoxy, hydroxy, amino, C₁-₆alkyl substituted with 0-2 R₆, C₂-₆alkenyl substituted with 0-2 R₆, C₂-₆alkynyl substituted with 0-2 R₆, C₁-₆alkoxy [substituted with 0-2 R₆], -NH(C₁-₆alkyl) substituted with 0-2 R₆, -N(C₁-₆alkyl)(C₁-₆alkyl) where each C₁-₆alkyl is independently substituted with 0-2 R₆, -XR₇, and Y;

R₉ represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C₁-₆)alkyl, halo(C₁-₆)alkoxy, hydroxy, amino, C₁-₆alkyl substituted with 0-2 R₆, C₂-₆alkenyl substituted with 0-2 R₆, C₂-₆alkynyl substituted with 0-2 R₆, C₁-₆alkoxy substituted with 0-2 R₆, and Y;

R₆ is independently selected at each occurrence from the group consisting of halogen, hydroxy, cyano, C₁-₄alkyl, C₁-₄alkoxy, [-NH(C₁-₄alkyl), -N(C₁-₄alkyl)(C₁-₄alkyl),] -S(O)_n(C₁-₄alkyl), halo(C₁-₄)alkyl, halo(C₁-₄)alkoxy, CO(C₁-₄alkyl), CONH(C₁-₄alkyl), CON(C₁-₄alkyl₁)(C₁-₄alkyl₂) where alkyl₁ and alkyl₂ may be joined to form a [heterocycloalkyl ring] heterocycle

of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, -XR₇, and Y;

X is independently selected at each occurrence from the group consisting of -CH₂-, -CHR₈-, -O-, -S(O)_n-, -NH-, -NR₈-, -C(=O)-, -C(=O)O-, -C(=O)NH-, -C(=O)NR₈-, -S(O)_nNH-, -S(O)_nNR₈-, NHC(=O)-, -NR₈C(=O)-, -NHS(O)_n-, and -NR₈S(O)_n;

R₇ and R₈ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms [may be further] is unsubstituted or substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(C₁₋₄alkyl), -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NHS(O)_n(C₁₋₄alkyl), -S(O)_n(C₁₋₄alkyl), -S(O)_nNH(C₁₋₄alkyl), -S(O)_nN(C₁₋₄alkyl₃)(C₁₋₄alkyl₄) where C₁₋₄alkyl₃ and C₁₋₄alkyl₄ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, halo(C₁₋₄)alkyl, halo(C₁₋₄)alkoxy, mono- or di(C₁₋₄)alkylamino, and C₁₋₄alkylthio; wherein said 3- to [8-memberered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

37. (Amended) A compound or salt according to Claim 32, wherein:

A represents NH;

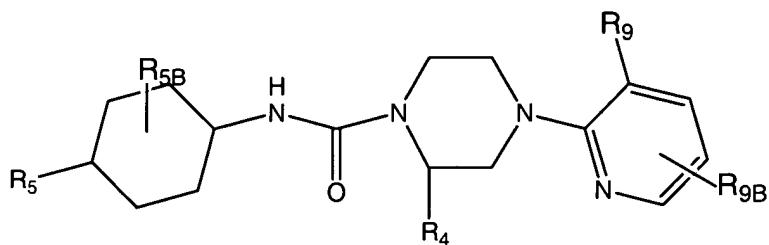
R₃ represents hydrogen;

R₄ is independently chosen at each occurrence from hydrogen and methyl; and

R₅ [and R₉ each represent] represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, [-NH(C₁₋₆alkyl] -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), and C₃₋₈ cycloalkyl; and

R₉ represents from 1 to 3 substituents independently selected at each occurrence from the group consisting of halogen, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, and C₃₋₈cycloalkyl.

38. (Amended) A compound or salt [according to Claim 37] of the Formula A-1



Formula A-1

wherein

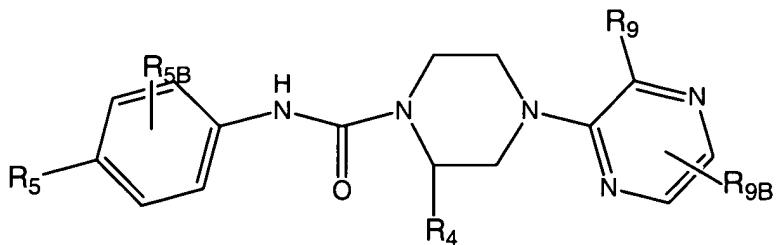
R₄ is hydrogen or methyl;

R₅ and R₉ are independently selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, [-NH(C₁₋₆alkyl)] -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), and C₃₋₈cycloalkyl; and

R_{5B} and R_{9B} each represent [up] from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy,

hydroxy, amino, C₁₋₃alkyl, C₁₋₃alkoxy, -NH(C₁₋₃alkyl), and -N(C₁₋₆alkyl)(C₁₋₆alkyl).

40. (Amended) A compound or salt [according to Claim 37] of Formula B-1



Formula B-1

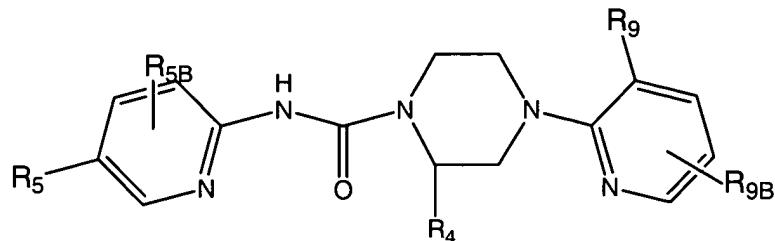
wherein

R₄ is hydrogen or methyl;

R₅ and R₉ are independently selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, [-NH(C₁₋₆alkyl)] -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), and C₃₋₈ cycloalkyl; and

R_{5B} and R_{9B} each represent [up] from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, hydroxy, amino, C₁₋₃alkyl, C₁₋₃alkoxy, -NH(C₁₋₃alkyl), and -N(C₁₋₆alkyl)(C₁₋₆alkyl).

42. (Amended) A compound or salt [according to Claim 37]
of Formula C-1[:]



Formula C-1

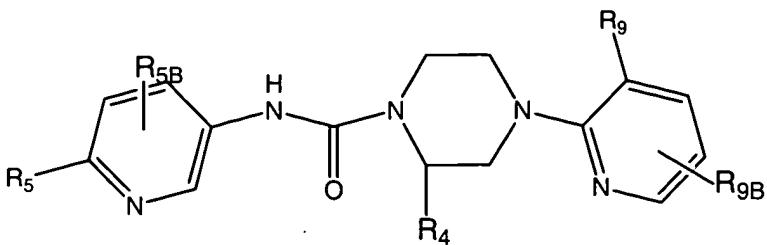
wherein:

R_4 is hydrogen or methyl;

R_5 and R_9 are independently selected from the group consisting of halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $[-\text{NH}(\text{C}_{1-6}\text{alkyl})-\text{NH}(\text{C}_{1-6}\text{alkyl})]$, $-\text{N}(\text{C}_{1-6}\text{alkyl})(\text{C}_{1-6}\text{alkyl})$, and C_{3-8} cycloalkyl; and

R_{5B} and R_{9B} each represent [up] from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C_{1-2})alkyl, halo(C_{1-2})alkoxy, hydroxy, amino, C_{1-3} alkyl, C_{1-3} alkoxy, $-\text{NH}(\text{C}_{1-3}\text{alkyl})$, and $-\text{N}(\text{C}_{1-6}\text{alkyl})(\text{C}_{1-6}\text{alkyl})$.

44. (Amended) A compound or salt according to Claim 37 of
Formula D-1



Formula D-1

wherein:

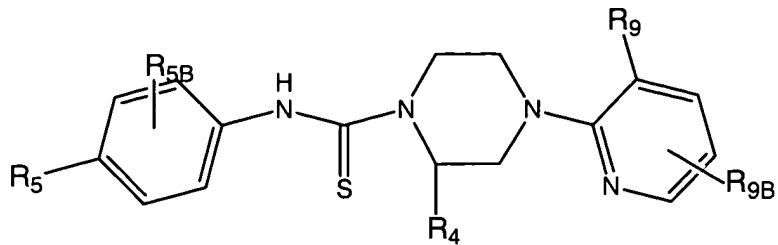
R₅ [and R₉ are independently] is selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, [-NH(C₁₋₆alkyl)] -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), and C₃₋₈ cycloalkyl;

R₉ is selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, and C₃₋₈ cycloalkyl; and

R_{5B} and R_{9B} each represent [up] from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, hydroxy, amino, C₁₋₃alkyl, C₁₋₃alkoxy, -NH(C₁₋₃alkyl), and -N(C₁₋₆alkyl)(C₁₋₆alkyl).

46. (Amended) A compound or salt [according to Claim 37,].

of Formula E-1



Formula E-1

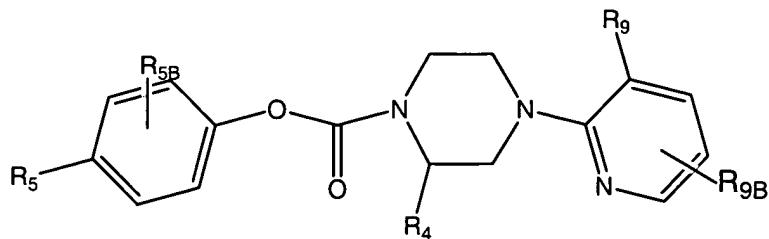
wherein:

R₄ is hydrogen or methyl;

R₅ and R₉ are independently selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, [-NH(C₁₋₆alkyl)] -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), and C₃₋₈ cycloalkyl; and

R_{5B} and R_{9B} each represent [up] from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, hydroxy, amino, C₁₋₃alkyl, C₁₋₃alkoxy, -NH(C₁₋₃alkyl), and -N(C₁₋₆alkyl)(C₁₋₆alkyl).

48. (Amended) A compound of salt [according to Claim 37] of Formula F-1



Formula F-1

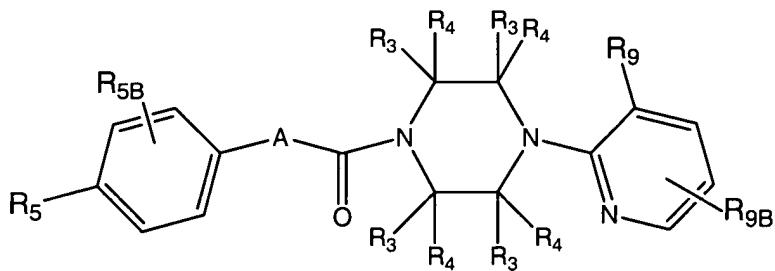
wherein:

R₄ is hydrogen or methyl;

R₅ and R₉ are independently selected from the group consisting of halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, [-NH(C₁₋₆alkyl) -NH(C₁₋₆alkyl)], -N(C₁₋₆alkyl)(C₁₋₆alkyl), and C₃₋₈ cycloalkyl; and

R_{5B} and R_{9B} each represent [up] from 0 to 2 substituents independently selected at each occurrence from hydrogen, halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, hydroxy, amino, C₁₋₃alkyl, C₁₋₃alkoxy, -NH(C₁₋₃alkyl), and -N(C₁₋₆alkyl)(C₁₋₆alkyl).

50. (Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', NR_ACR_BR_B', CR_B R_B'NR_A, -CR_A=CR_B-, and C₃H₄; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen [or] and C₁₋₆ alkyl;

each R₃ and R₄ [are] is independently

(a) selected [at each occurrence] from the group consisting of hydrogen, halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl substituted with 0-2 R₆, C₂₋₆alkenyl substituted with 0-2 R₆; C₂₋₆alkynyl substituted with 0-2 R₆; C₁₋₆alkoxy substituted with 0-2 R₆, -NH(C₁₋₆alkyl) substituted with 0-2 R₆, -N(C₁₋₆alkyl)(C₁₋₆alkyl) where each C₁₋₆alkyl is independently substituted with 0-2 R₆, -XR₇, and Y; or

(b) [any two] joined to a R₃ [and] or R₄ not attached to the same carbon [may be joined] to form an aryl ring substituted with 0-3 R₆, a saturated or partially unsaturated carbocyclic ring of from 5 to 8 members, which carbocyclic ring is substituted with 0-2 R₆, or a saturated, partially unsaturated, or aromatic heterocyclic ring of from 5 to 8 members, which heterocyclic ring is substituted with 0-2 R₆ and contains 1, 2, or 3 heteroatoms independently selected from N, O, and S;

R_5 is selected from the group consisting of bromo, fluoro, iodo, halo(C_{1-6})alkyl, halo(C_{3-6})alkoxy, C_{3-6} alkyl substituted with 0-3 R_6 , C_{2-6} alkenyl substituted with 0-3 R_6 , C_{2-6} alkynyl substituted with 0-3 R_6 , C_{3-6} alkoxy [substituted with 0-2 R_6], (C_{3-8} cycloalkyl) C_{1-4} alkyl, $-NH(C_{1-6}$ alkyl) substituted with 0-2 R_6 , $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) where each C_{1-6} alkyl is substituted with 0-2 R_6 , Y , $-(C=O)Y$, $-(CH_2)Y$, and $-(CH(CN))Y$;

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2C_{1-6}$ alkyl)(SO_2C_{1-6} alkyl), $-SO_2NH_2$, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, C_{1-6} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 , C_{2-6} alkynyl substituted with 0-2 R_6 , and C_{1-6} alkoxy substituted with 0-2 R_6 [$, -NH(C_{1-6}$ alkyl) substituted with 0-2 R_6 , $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) where each C_{1-6} alkyl is substituted with 0-2 R_6];

R_{5B} [and R_{9B} each represent] represents from 0 to 2 substituents [and are] independently selected at each occurrence from the group consisting of

(a) halogen, cyano, nitro, halo(C_{1-6})alkyl, halo(C_{1-6})alkoxy, hydroxy, amino, C_{1-6} alkyl substituted with 0-2 R_6 , (C_{3-8} cycloalkyl) C_{1-4} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 , C_{2-6} alkynyl substituted with 0-2 R_6 , C_{1-6} alkoxy [substituted with 0-2 R_6], $-NH(C_{1-6}$ alkyl) substituted with 0-2 R_6 , [and] $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl) where

each C_{1-6} alkyl is independently substituted with 0-2 R_6 , and Y ; and [any two R_5 and R_{5B} bound to adjacent atoms may be]

(b) groups that are joined to R_5 to form a C_{3-8} cycloalkyl group or a [heterocycloalkyl group] saturated or partially unsaturated heterocycle, each of which is optionally substituted by from 1 to 5 substituents independently chosen from cyano, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, - $NH(C_{1-4}$ alkyl), - $N(C_{1-4}$ alkyl)(C_{1-4} alkyl), $halo(C_{1-4})$ alkyl, and $halo(C_{1-4})$ alkoxy, wherein the [heterocycloalkyl group] saturated or partially unsaturated heterocycle [consists of] contains from 4 to 8 ring atoms [and contains] of which 1, 2, or 3 are heteroatoms independently selected from N, O, and S;

R_{9B} represents from 0 to 2 substituents independently selected at each occurrence from halogen, cyano, nitro, $halo(C_{1-6})$ alkyl, $halo(C_{1-6})$ alkoxy, hydroxy, amino, C_{1-6} alkyl substituted with 0-2 R_6 , $(C_{3-8}$ cycloalkyl) C_{1-4} alkyl substituted with 0-2 R_6 , C_{2-6} alkenyl substituted with 0-2 R_6 , C_{2-6} alkynyl substituted with 0-2 R_6 , C_{1-6} alkoxy substituted with 0-2 R_6 , and Y ;

R_6 is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, [- $NH(C_{1-4}$ alkyl), - $N(C_{1-4}$ alkyl)(C_{1-4} alkyl),] - $S(O)_n(C_{1-4}$ alkyl), $halo(C_{1-4})$ alkyl, $halo(C_{1-4})$ alkoxy, $CO(C_{1-4}$ alkyl), $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl $_1$)(C_{1-4} alkyl $_2$) where alkyl $_1$ and alkyl $_2$

may be joined to form a [heterocycloalkyl ring] heterocycle of from 5 to 8 ring atoms and containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, -XR₇, and Y;

X is independently selected at each occurrence from the group consisting of -CH₂-, -CHR₈-, -O-, -S(O)_n-, -NH-, -NR₈-, -C(=O)-, -C(=O)NH-, -C(=O)NR₈-, -S(O)_nNH-, -S(O)_nNR₈-, NHC(=O)-, -NR₈C(=O)-, -NHS(O)_n-, and -NR₈S(O)_n;

R₇ and R₈ are independently selected at each occurrence from hydrogen, and straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups, said straight, branched, and cyclic alkyl groups, and (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, and containing zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy, halogen, amino, cyano, nitro, haloalkyl, haloalkoxy, -O(C₁₋₄alkyl), NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)(C₁₋₄alkyl), -NHC(O)(C₁₋₄alkyl), -N(C₁₋₄alkyl)C(O)(C₁₋₄alkyl), -NHS(O)_n(C₁₋₄alkyl), -S(O)_n(C₁₋₄alkyl), -S(O)_nNH(C₁₋₄alkyl), -S(O)_nN(C₁₋₄alkyl₃)(C₁₋₄alkyl₄) where C₁₋₄alkyl₃ and C₁₋₄alkyl₄ [may be] are optionally joined to form a [heterocycloalkyl ring] heterocycle consisting of from 5 to 8 ring atoms and

containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, and Y';

Y and Y' are independently selected at each occurrence from 3- to 8-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, halo(C₁₋₄)alkyl, halo(C₁₋₄)alkoxy, mono- or di(C₁₋₄)alkylamino, and C₁₋₄alkylthio;

wherein said 3- to [8-memberered] 8-membered heterocyclic groups contain one or more heteroatom(s) independently selected from N, O, and S; and

n is independently chosen at each occurrence from 0, 1, and 2.

59. (Amended) A compound or salt according to Claim 58 wherein:

R₉ is selected from the group consisting of halogen, cyano, -N(SO₂CH₃)₂, -SO₂NH₂, halo(C₁₋₃)alkyl, and C₁₋₃alkoxy [, -NH(C₁₋₃alkyl), and -N(C₁₋₃alkyl)(C₁₋₃alkyl)].

62. (Amended) A compound or salt according to Claim 57, wherein:

R₉ is selected from the group consisting of halogen, cyano, -

N(SO₂CH₃)₂, -SO₂NH₂, halo(C₁₋₃)alkyl, and C₁₋₃alkoxy [, -NH(C₁₋₃)alkyl], and -N(C₁₋₃alkyl)(C₁₋₃alkyl)];

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, amino, C₁₋₄alkyl, and C₁₋₂alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C₁₋₂)alkyl, [and] C₁₋₂alkyl, and C₁₋₂alkoxy.

63. (Amended) A compound or salt according to Claim 57,

wherein:

R₅ is selected from the group consisting of bromo, fluoro, iodo, halo(C₁₋₆)alkyl, halo(C₃₋₆)alkoxy, C₃₋₆alkyl substituted with 0-3 R₆, C₂₋₆alkenyl substituted with 0-3 R₆, Y, -(C=O)Y, -(CH₂)Y, and -(CH(CN))Y;

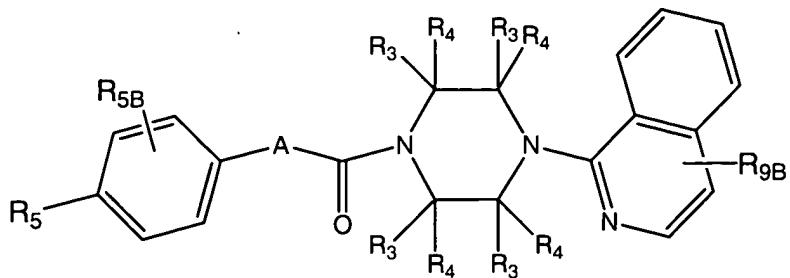
R₉ is selected from the group consisting of halogen, cyano, -

N(SO₂CH₃)₂, -SO₂NH₂, halo(C₁₋₂)alkyl, and C₁₋₃alkoxy [, -NH(C₁₋₆)alkyl], and -N(C₁₋₆alkyl)(C₁₋₆alkyl)];

R_{5B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, amino, C₁₋₄alkyl, and C₁₋₂alkoxy; and

R_{9B} represents 0 or 1 substituents chosen from halogen, cyano, nitro, halo(C₁₋₂)alkyl, [and] C₁₋₂alkyl, and C₁₋₂alkoxy.

161. (Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O, S, NR_A, CR_BR_B', NR_ACR_BR_B', CR_BR_B'NR_A, -CR_A=CR_B-, and C₃H₄; where R_A, R_B, and R_B' are independently selected at each occurrence from hydrogen [or] and C₁₋₆ alkyl;

R₃ and R₄ are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, hydroxy, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, -NH(C₁₋₆alkyl), and -N(C₁₋₆alkyl)(C₁₋₆alkyl);

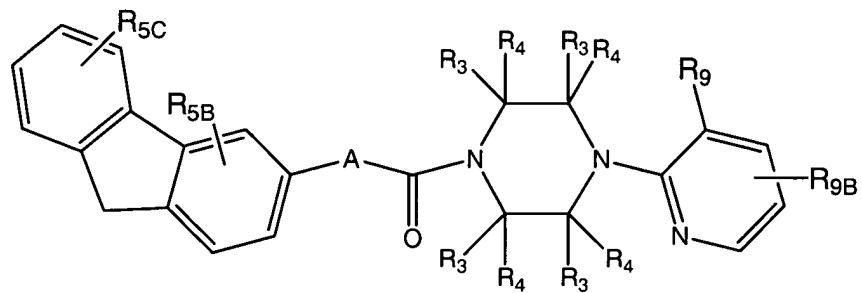
R₅ is selected from the group consisting of halogen, halo(C₁₋₆)alkyl, C₃₋₆alkyl substituted with 0-3 R₆, C₂₋₆alkenyl substituted with 0-3 R₆, (C₃₋₈cycloalkyl)C₁₋₄alkyl substituted with 0-3 R₆, and Y;

R_{5B} and R_{9B} each represent from 0 to 2 substituents and are independently chosen from halogen, cyano, nitro, halo(C₁₋₂)alkyl, halo(C₁₋₂)alkoxy, amino, C₁₋₄alkyl, and C₁₋₂alkoxy;

R_6 is independently selected at each occurrence from the group consisting of cyano, halogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, $-NH(C_{1-4}\text{alkyl})$, [and] $-N(C_{1-4}\text{alkyl})(C_{1-4}\text{alkyl})$ and Y ;

Y is independently selected at each occurrence from C_{3-8} cycloalkyl, piperidinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, morpholinyl, thiomorpholinyl, phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, thietyl, and imidazolyl, each of which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy, amino, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, mono- or di(C_{1-4})alkylamino, and C_{1-4} alkylthio.

169. (Amended) A compound of the Formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is absent or is selected from the group consisting of O , S , NR_A , CR_BR_B' , $NR_ACR_BR_B'$, $CR_BR_B'NR_A$, $-CR_A=CR_B-$, and C_3H_4 ; where

R_A , R_B , and R_B' are independently selected at each occurrence from hydrogen [or] and C_{1-6} alkyl;

R_3 and R_4 are independently chosen at each occurrence from the group consisting of hydrogen, halogen, cyano, nitro, $halo(C_{1-6})alkyl$, $halo(C_{1-6})alkoxy$, hydroxy, amino, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{1-6}alkoxy$, $-NH(C_{1-6}alkyl)$, and $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$;

R_{5B} , R_{5C} , and R_{9B} each represent from 0 to 2 substituents and are independently chosen from halogen, cyano, nitro, $halo(C_{1-2})alkyl$, $halo(C_{1-2})alkoxy$, amino, $C_{1-4}alkyl$, and $C_{1-2}alkoxy$; and

R_9 is selected from the group consisting of halogen, cyano, $-N(SO_2CH_3)_2$, $-SO_2NH_2$, $halo(C_{1-3})alkyl$, $C_{1-3}alkoxy$, $-NH(C_{1-3}alkyl)$, and $-N(C_{1-3}alkyl)(C_{1-3}alkyl)$.